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Physiological and anatomical evidence for a magnocellular defect in developmental dyslexia

(visual perception/magnocellular geniculate/parvocellular geniculate)

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ABSTRACT **Several behavioral studies have shown that developmental dyslexics do poorly in tests requiring rapid visual processing. In primates fast, low-contrast visual information is carried by the magnocellular subdivision of the visual pathway, and slow, high-contrast information is carried by the parvocellular division. In this study, we found that dyslexic subjects showed diminished visually evoked potentials to rapid, low-contrast stimuli but normal responses to slow or high-contrast stimuli. The abnormalities in the dyslexic subjects' evoked potentials were consistent with a defect in the magnocellular pathway at the level of visual area 1 or earlier. We then compared the lateral geniculate nuclei from five dyslexic brains to five control brains and found abnormalities in the magnocellular, but not the parvocellular, layers. Studies using auditory and somatosensory tests have shown that dyslexics do poorly in these modalities only when the tests require rapid discriminations. We therefore hypothesize that many cortical systems are similarly divided into a fast and a slow subdivision and that dyslexia specifically affects the fast subdivisions.**

Developmental dyslexia is the selective impairment of reading skills despite normal intelligence, sensory acuity, motivation, and instruction. Several perceptual studies have suggested that dyslexic subjects process visual information more slowly than normal subjects. The flicker fusion rate, which is the fastest rate at which a contrast reversal of a stimulus can be seen, is abnormally slow in dyslexic children at low spatial frequencies and low contrasts (1). Moreover, such visual abnormalities were reported to be found in >75% of the reading-disabled children tested (2). When two visual stimuli are presented in rapid succession, the two images fuse and appear as a single presentation; the temporal separation necessary to distinguish two presentations measures visual persistence, and this is up to 100 msec longer for dyslexic than for normal children, particularly for low spatial frequency stimuli (3–6). Dyslexic subjects also have trouble distinguishing the order of two rapidly flashed visual stimuli (7). In contrast, dyslexics perform normally on tests having prolonged stimulus presentations (2).

These perceptual studies suggest an abnormality in dyslexia affecting some part of the visual system that is fast and transient and has high contrast sensitivity and low spatial selectivity. Exactly these properties characterize the magnocellular subdivision of the visual pathway (8, 9). The primate visual system is composed mainly of two major processing pathways that remain largely segregated and independent throughout the visual system. This subdivision begins in the retina but is most apparent in, and was first discovered in, the lateral geniculate nucleus (LGN), where cells in the ventral, or magnocellular, layers are larger than cells in the dorsal, or parvocellular, layers. In the retina and the LGN, the magno and parvo subdivisions differ physiologically in four major ways: color selectivity, contrast sensitivity, temporal resolution, and acuity (8, 9). This functional segregation, begun in the retina, continues throughout the visual system, possibly even up through higher cortical association areas. Therefore a problem specific to the magnocellular pathway could originate at any level from the retina to prestriate visual cortical areas, and it would be difficult, using behavioral tests, to localize such perceptual defects.

In this study, we used physiological rather than behavioral methods to measure the visual temporal resolution and contrast sensitivity of normal and dyslexic adult subjects, and we have correlated these physiological results with anatomical observations in autopsy specimens.

MATERIALS AND METHODS

A total of five dyslexic and seven normal subjects participated in the visually evoked potential (VEP) studies. Only four dyslexic and six normal subjects were tested with the 0.5-Hz stimulus (transient pattern reversal VEP). The dyslexic subjects (three males and two females; mean age, 27.4 ± 3.8 years) all had been formally diagnosed and were of above average intelligence. The control subjects (four males and three females; mean age, 25.8 ± 4.5 years) were all normal readers and were matched to the dyslexic subjects in age, intelligence, education, and professional level. Coppercup surface electrodes were placed at OZ (90% of the distance from nasion to inion) and at CZ (reference electrode, 50% of the distance from nasion to inion) (10). Stimuli were generated by a Grass visual pattern generator, model 10VPG, on a Grass model VPGM black and white monitor with a 60-Hz refresh rate. The stimulus consisted of a rectangular checkerboard (24 × 18.5 cm) of 36 rectangles (each 4 × 3 cm) presented at a viewing distance of 60 cm. (Spatial frequency was thus 0.16 cycle per degree vertically and 0.12 cycle per degree horizontally.) The contrast of the checkerboard was reversed in a counterphase squarewave temporal pattern at 0.5 Hz (1 contrast reversal per sec) for the transient VEP and at various frequencies for the steady-state VEP. Responses were triggered by the stimulus contrast reversal and recorded and averaged with a Grass Bio-response averager, model BA10CD. The signals were amplified 20,000 times and filtered with a low-frequency cut-off of 1 Hz and a high-frequency cut-off of 100 Hz. The light intensity of the monitor was measured with an SIE photometer, and, for all contrasts tested, the luminance averaged over the entire stimulus was

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Abbreviations: VEP, visually evoked potential; LGN, lateral geniculate nucleus.

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4.0 cd/m^2. Contrast is expressed as a Michelson fraction—$(L_{max} - L_{min})/(L_{max} + L_{min})$.

We examined the LGN in autopsy specimens from five dyslexic subjects (four males and one female; mean age, 34.2 ± 13.7 years) and five nondyslexic subjects (all males; mean age, 40 ± 11.2 years). All of the dyslexic brains came from subjects who were diagnosed in life and had been used in previous anatomical studies (11, 12). The control subjects had had sufficient testing during life to permit exclusion of the diagnosis of developmental dyslexia. We used the Yakovlev method for processing whole brains in serial histological sections (13). Brains were sectioned at 35 μm, and every 20th section was stained for Nissl substance with cresylechviolett.

Images representing the medial, middle, and lateral portions of parvocellular and magnocellular layers were digitized (512 × 512 × 8) using a Gould FD-5000 image analysis system interfaced to a DEC VAX 11/750 computer. For each image, the observer selected a gray-level threshold so that most of the Nissl-stained neurons were fully filled. Using this threshold, object borders were drawn using an artificial intelligence-based algorithm, and the observer then selected for automated measurement every isolated object that was fully filled and was identifiable by morphology as a neuron.

RESULTS

We used physiological methods to compare the contrast sensitivity and temporal resolution of normal and dyslexic adult subjects. We recorded visually evoked potentials to the contrast reversal of a binocularly presented checkerboard pattern at both low and high contrasts (Fig. 1). At a contrast of 0.2, the VEP looked similar for the normal and dyslexic groups. At the lower contrast of 0.02, however, the dyslexics' VEP showed early differences that could be interpreted as a 20- to 40-msec delay in a small broad negative wave, which in the normal subjects peaked around 50 msec. The early phase of the evoked response is quite variable between subjects and under different stimulus conditions (14) so it is difficult to interpret the differences we found, but it has been suggested that the earliest negative wave of the contrast appearance-evoked potential represents activity in the magnocellular system because it shows high contrast sensitivity and is maximum at low spatial frequencies (15). In all the normal subjects we tested, at low contrasts the earliest component of the VEP was negative-going, and in all the dyslexic subjects tested this component was missing or delayed. Although anatomical substrates of the VEP are poorly understood, the early negative wave of the pattern-reversal VEP probably reflects activity in thalamo-recipient layer 4C of visual area 1 (16–18). The dyslexic subjects also showed a delay in the large positive wave normally peaking around 100 msec, as well as differences at longer times that are uninterpretable.

Since differences in transient VEPs are not easily interpreted or quantified, we decided to look at steady-state evoked potentials to rapidly alternating patterns, because the sinusoidal shape of the wave allows simple measurement of the amplitude of the response (19). We recorded responses to alternating counterphase contrast reversals of the same checkerboard pattern at several frequencies and contrasts (Fig. 2). At high contrasts, the VEP for all subjects showed oscillatory responses, phase-locked to the visual stimulus. At 15 Hz the responses of the normal subjects to low-contrast stimuli were slightly reduced, but the responses of the dyslexic subjects almost disappeared. Fourier spectra of these responses (Fig. 3) showed that at contrasts of 0.01 and 0.02 the dyslexic subjects produced significantly smaller responses to a 15-Hz stimulus ($P < 0.01$; Mann–Whitney U test) but normal responses to slower stimulation frequencies or to higher contrast at all stimulating frequencies. Since cells in the magno system respond well to low-contrast stimuli, and cells in the parvo system do not (8, 9), this result suggests that the magno system of dyslexics can respond to low-contrast stimuli, but the response is simply slower than normal, consistent with the apparent delays in the early components of the evoked response. The normal responses of the dyslexic subjects to the 15-Hz stimulus at higher contrast could be accounted for by a speeding up of their magno system at high contrasts or to a high frequency response of the parvo system. We have no way to distinguish between these two possibilities since in monkeys the magno system does respond more rapidly at high contrasts than at low contrasts (9, 20), but at high contrasts the parvo system can also respond to frequencies as fast as 15 Hz (20, 21).

Our VEP results thus suggest an abnormality in the magnocellular pathway at the level of visual area 1 or earlier. We therefore examined Nissl-stained sections of the LGN from autopsy material from five dyslexic and five nondyslexic subjects. On inspection, the parvocellular layers appeared similar in the two groups, but the magnocellular layers were more disorganized in the dyslexic brains, and the cell bodies appeared smaller. A computerized image analysis system was used to measure cell body area. For three independent observers (two blind as to the identity of the subjects) both the mean and median magnocellular areas were significantly smaller (on average, 27% smaller) in the dyslexic brains ($P < 0.05$ in all cases, repeated measures analysis of variance; Table 1 and Fig. 4). There were no significant differences between controls and dyslexics in the cell sizes in the parvocellular layers, which excludes any systematic differ-

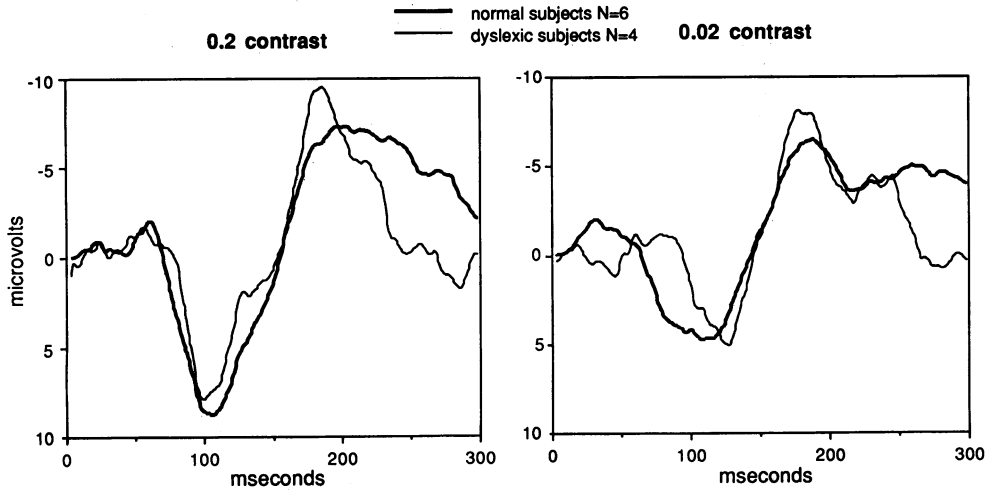

FIG. 1. Averaged visually evoked responses from normal and dyslexic subjects. For each subject at each contrast 128 responses were averaged. Then the responses from six normal and four dyslexic subjects were scanned and digitized, and the results for each group were averaged together. Negative is upward.

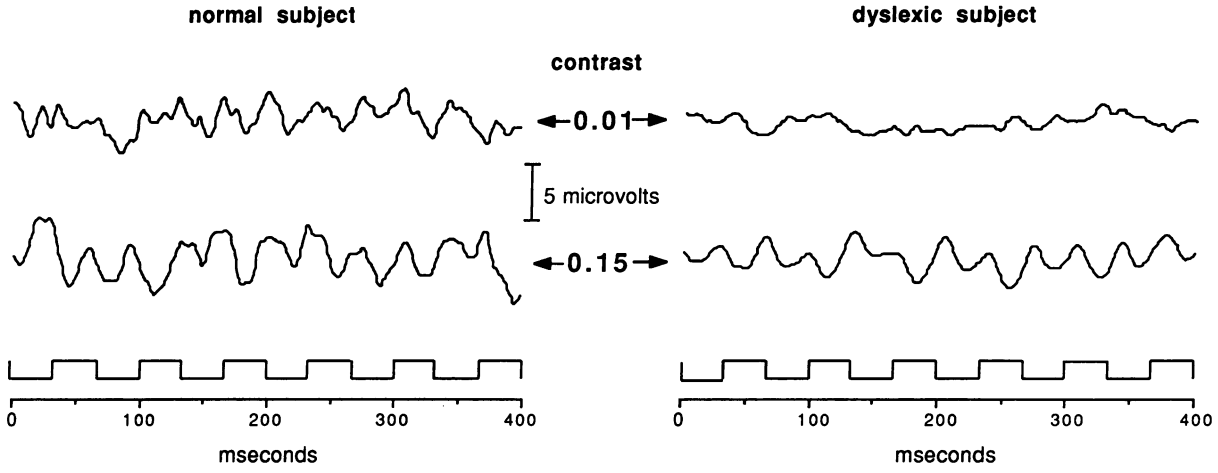

FIG. 2. Examples of cortical evoked responses in two individual subjects, a control and a dyslexic, to 15-Hz contrast reversal of the same checkerboard pattern as in Fig. 1. Negative is upward. As shown in the lower trace, which indicates the luminance of one square in the checkerboard pattern, the contrast of the checkerboard was reversed in a counterphase squarewave temporal pattern at 15 Hz (30 contrast reversals per sec). Each tracing is the average of 64 sweeps. Note that the dyslexic subject shows a much reduced response at a contrast of 0.01.

ences in the degree of tissue shrinkage or staining between the two groups ($F_{(1,8)} < 1$ in all cases).

The decreased size of the magnocellular geniculate neurons might be expected to have functional consequences that are consistent with our physiological findings: smaller cell bodies are likely to have thinner axons, which should have slower conduction velocities. These abnormalities might be magnified if there were also defects at earlier or later stages in the magnocellular pathway.

DISCUSSION

Physiological studies indicate that the magno system carries information about motion and stereopsis, and human perceptual studies suggest that it may also be responsible for spatial localization, depth perception, hyperacuity, figural grouping, illusory border perception, and figure/ground segregation (22). The observations that dyslexics often have poor stereoacuity (23), visual instability, and problems in visual localization (24) are consistent with a problem in the magnocellular pathway. Moreover, reading is difficult for normal subjects when the letters and background are different colors but have no luminance contrast, a condition under which the magno system responds very poorly (22, 42).

The role of the magnocellular system in reading is unknown, but it has been suggested (25, 26) that after each saccade the magnocellular system must inhibit the parvocellular system, erasing the otherwise persistent image of the previous fixation. Another possibility, perhaps related, is raised by the finding that the magnocellular system may be essential for maintaining positional stability during saccades (25, 27).

Many authors have argued that dyslexia is a specifically linguistic problem arising from a poor understanding of the

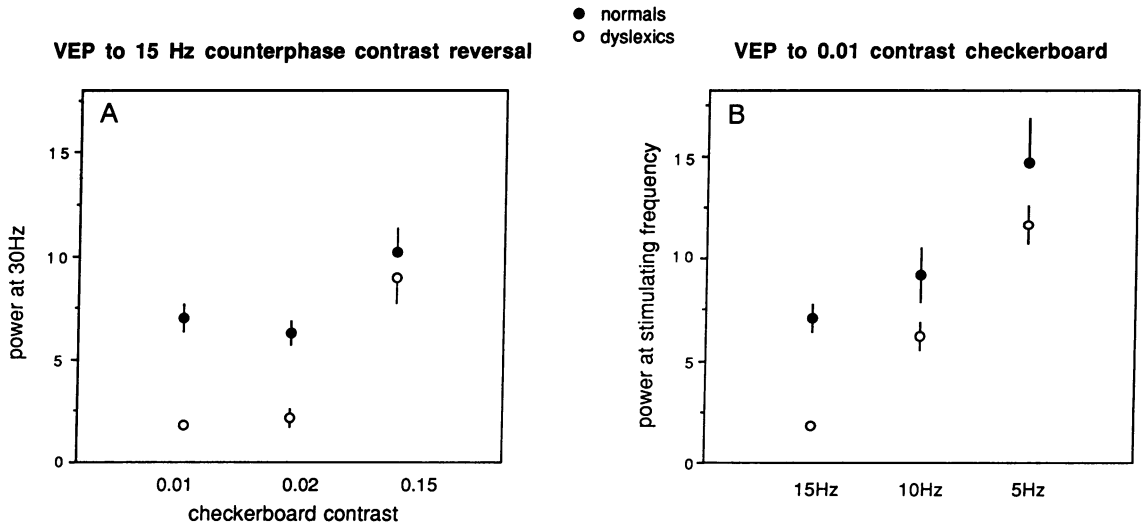

FIG. 3. Fourier spectrum analyses of evoked potentials, such as those shown in Fig. 2, at different contrasts and stimulation frequencies for seven normal subjects and five dyslexic subjects. For each subject, and for each contrast level and stimulus frequency, 64 sweeps were averaged, then each response was scanned and digitized, and a Fourier spectrum was calculated. The ordinate indicates the power in the Fourier spectrum at the same frequency as the contrast reversal rate (twice the stimulus cycle rate) of the visual stimulus. Values indicate means ± SEM. We used a Mann–Whitney U test to determine that the responses of the dyslexic and normal populations differed significantly for the two lowest contrasts at 15 Hz (z value for 0.01 contrast = −2.3; z value for 0.02 contrast = −2.6; for both contrasts, $P < 0.01$). The normal responses of the dyslexic subjects to the 15-Hz stimulus at 0.15 contrast could be accounted for either by a speeding up of their magno system at high contrasts or by a high frequency response of the parvo system, and we cannot distinguish between these possibilities.

Table 1. Mean and median cell areas from the magnocellular and parvocellular layers of the LGN of dyslexic and nondyslexic brains for all three observers (Obs.)

		Magnocellular			Parvocellular		
Subject	Obs.	Mean ± SEM	Median	*n*	Mean ± SEM	Median	*n*
			Dyslexics				
Ort-01	1	254.70 ± 6.45	235.30	339	195.91 ± 3.28	182.05	642
	2	305.43 ± 7.96	287.55	304	238.92 ± 3.98	226.90	559
	3	252.38 ± 6.09	248.05	248	169.34 ± 2.32	162.30	428
Ort-02	1	349.57 ± 7.40	334.30	409	182.57 ± 2.59	170.60	813
	2	380.02 ± 7.81	359.90	367	193.70 ± 2.64	181.30	827
	3	332.75 ± 6.71	325.45	350	155.69 ± 1.87	147.40	742
Ort-05	1	207.52 ± 3.96	203.20	430	134.56 ± 1.55	126.90	895
	2	262.93 ± 5.00	252.50	483	159.91 ± 1.63	150.60	1124
	3	238.64 ± 3.80	229.70	441	144.98 ± 1.42	140.40	847
Ort-20	1	325.86 ± 7.89	299.20	292	225.62 ± 3.46	213.65	564
	2	363.52 ± 8.43	352.65	276	234.92 ± 3.72	228.30	698
	3	316.70 ± 6.41	309.45	300	174.56 ± 2.02	172.00	670
Ort-30	1	283.87 ± 7.23	266.40	428	233.41 ± 3.78	217.10	713
	2	292.03 ± 5.96	271.10	461	207.49 ± 2.51	196.20	779
	3	251.02 ± 4.82	238.30	446	179.20 ± 1.93	173.90	597
			Controls				
Ort-07	1	395.96 ± 8.01	385.90	283	157.33 ± 1.88	153.40	776
	2	407.40 ± 8.90	400.10	288	204.21 ± 2.62	194.80	799
	3	364.84 ± 7.09	346.15	292	140.66 ± 1.42	135.80	861
Ort-09	1	400.67 ± 11.03	388.45	216	197.15 ± 2.52	193.40	744
	2	396.97 ± 10.36	392.90	229	233.26 ± 3.44	222.70	722
	3	345.27 ± 7.16	338.25	284	185.03 ± 2.19	179.00	699
Ort-15	1	418.39 ± 11.71	396.40	142	197.00 ± 3.30	190.85	572
	2	358.47 ± 9.69	347.30	208	194.61 ± 2.84	182.70	789
	3	334.26 ± 7.31	310.35	254	156.50 ± 1.99	148.30	682
Ort-18	1	390.26 ± 7.08	388.25	300	183.52 ± 2.65	178.50	674
	2	369.48 ± 6.35	360.30	429	213.86 ± 2.90	203.70	850
	3	329.76 ± 5.02	333.35	394	179.94 ± 2.23	177.35	558
STD-B1	1	325.86 ± 7.89	299.20	292	225.62 ± 3.46	213.65	564
	2	387.35 ± 8.40	362.20	263	186.79 ± 2.32	174.80	932
	3	348.93 ± 7.62	335.70	260	170.54 ± 1.85	165.10	729

phonological structure of words (28–30). Linguistic deficits may, however, be related to perceptual problems since many phonemic discriminations involve rapid auditory transitions, and dyslexic and dysphasic children experience difficulties distinguishing nonlinguistic as well as linguistic auditory stimuli with rapid (≈40 msec) auditory transitions, but they perform normally with slower stimuli, both linguistic and nonlinguistic (31–34).

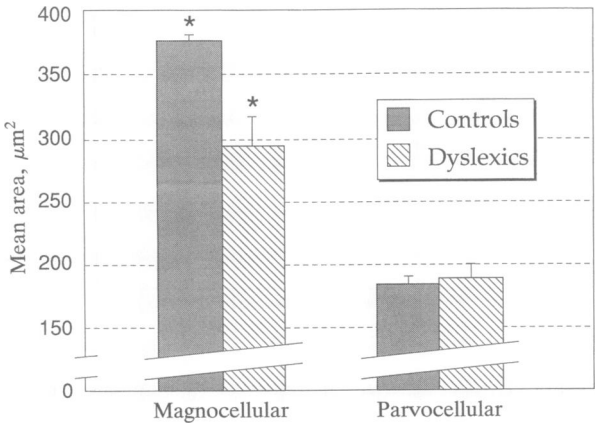

FIG. 4. Histological findings in control and dyslexic autopsy brains. The histograms show mean cell areas in the magnocellular and parvocellular layers of dyslexic and control LGN. The data are summed over all observers. *, $P < 0.05$, for all observers, repeated measures analysis of variance.

Other cortical systems exhibit functional segregation (35–37), and it is likely that they also have fast and slow subdivisions. This is particularly likely in light of the observations of McGuire *et al.* (38), who found that an antibody, CAT 301, selectively stains the magnocellular subdivision of the visual pathway, from the LGN through primary and secondary visual cortices up through higher parietal visual areas. This same antibody stains many other cortical areas, including some, but not all, somatosensory areas, a subset of the motor areas, and many other less well defined areas. Most of these areas differ from areas that do not stain with CAT 301 in that they are heavily myelinated, suggesting that they all have in common the ability to process information rapidly. The neuronal subdivisions involved in fast information processing in each modality thus may share particular molecular entities and might thereby be vulnerable to the same pathogenic factors. We hypothesize that in dyslexics the rapid subdivisions (the magnocellular homologues) of many forebrain systems might be slower than normal. Indeed, in behavioral tests, Tallal *et al.* (39) have shown that 98% of language-impaired children (children who have trouble learning to speak as well as read) could be differentiated from controls based solely on a battery of tests that require rapid speech production or rapid perceptual discriminations, both somatosensory and auditory.

Earlier studies of these same autopsy specimens (11, 12) reported anomalous cerebral asymmetry of a language area known as the planum temporale and developmental abnormalities of this and other language areas. Normal acquisition of phonological competence may depend on normal auditory perception at critical developmental times, and the anatomy

of the language areas may be modified by abnormal early sensory input (40, 41). On the other hand, the pathologic factors that disturb the magno subdivision of the visual pathway may also act directly on the development of the language areas themselves. Indeed, the language areas of the planum temporale are characterized by the presence of large pyramidal cells and rich myelination and may form part of the fast components of the auditory system.

Informed consent was obtained from all of our subjects after the nature and possible consequences of the study had been fully explained. Antis Zalkans processed the human specimens for histological analysis. Rita Burke and Jane McGuiggin provided technical help with the evoked potentials. William H. Baker, Jr., and the Orton Dyslexia Society helped establish access to brain donors for this project. We also thank an anonymous referee for helpful comments and the Office of Naval Research and the Orton Dyslexia Society for support.

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